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A bioinformatics approach for the interrogation of molecular events in single cells: transforming fluorescent time-lapse microscopy images into numbers

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Exploring and exploiting the enormous potential for pharmacological modulation of the mammalian cell cycle are key goals for basic research and drug discovery. We have developed a critical advance – the high temporal resolution monitoring of cell cycle progression enabling the tracking of single cell checkpoint transitions in a non-invasive manner even within heterogeneous populations. The green fluorescent protein (GFP)-based probe has expression, location and destruction characteristics that shadow cyclin B1 dynamics in living cells [1]. The non-perturbing stealth reporter performance has been validated on high content to high throughput detection platforms comprising multi-well high-throughput screen (HTS) imaging, single cell kinetic-tracking and multi-parameter flow cytometry [1,2]. Cyclin B1-GFP tracking provides sub-phase information on cell cycle progression, cell-cycle regulator dynamics in parallel with morphological landmarks and DNA content analysis. We have developed a bioinformatics software – FluroTRAK that semi automatically tracks the continuous progression of cell cycle traverse and encodes molecular readouts in bifurcating lineages. Single cell lineages which underlie the basic concept provide an elegant assay for determining the evolving and complex interplay for tumour survival at the single cell level. Our primary premise is that a bioinformatics approach dedicated to cell-based measurements provides an essential route to determining inter-event relationships revealing novel cellular and molecular event patterns.

Therefore our overall aim is to develop an integrated bioinformatics environment which encompasses the analysis tools to encode microscopy images into numbers and deposits the encoded data into relational databases. The intention is to provide a web-based interface with access to a suite of databases called CyMART http://biodiversity.cs.cf.ac.uk/cymart/ these provide databases enable robust hypothesis-driven data-mining and drug signature queries.

Conclusion

In the current study we describe a novel cell lineage encoding method that has enabled us to parametise molecular signatures derived from a stealth fluorescence reporter on a cell bifurcation map that represents cellular proliferation phenotypic responses. FluroTRAK provides a step change in our ability to encode and access information on multi-scalar dynamic cell behaviour. We believe that kinetic measurements provide an essential route to revealing important time windows and informative cells

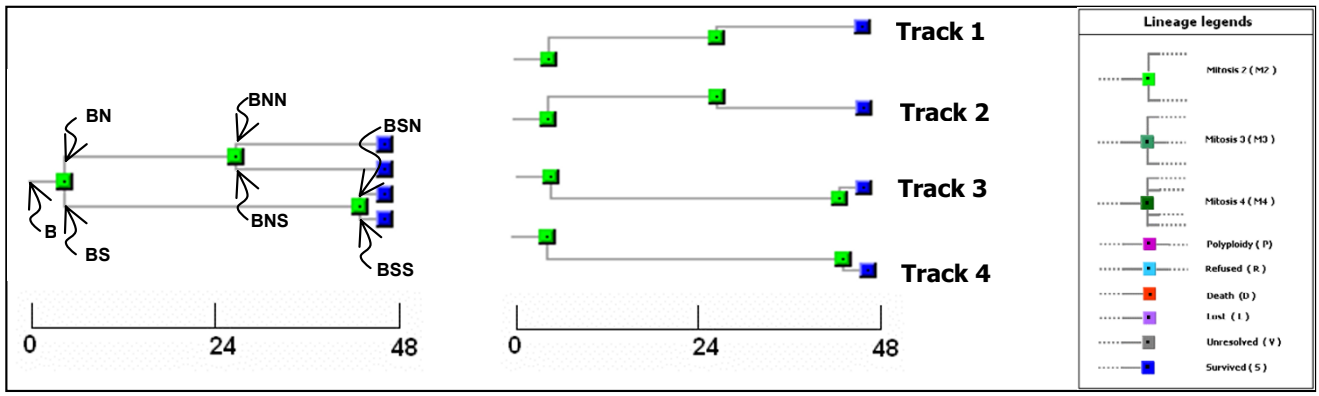

Figure 1

A typical encoded cell lineage. A cell lineage encoded from the progenitor cell (B), where the cell divides into two daughter cells 5 hours after the start of the experiment. The north daughter (BN) again divides at 28 hours into two daughter cells BNN and BNS while the south daughter BS divides at 44.66 hours into two daughter cells BSN and BSS. Four living cells (BNN,BNS, BSN and BSS) at the end of the experiment yielded four tracks labelled as track 1 2 3 and 4 respectively. Molecular readouts for each track encoded by the software and novel data format provides intra and inter lineage data relationship.

to study the mechanism of action of individual pharmacological agents and their response pathways. This encoding process encapsulates the critical features of cell-cell heterogeneity, molecular dynamics, phenotypic behaviour and time-dependent events. The multi-level descriptors and parameters attributed to each cell (and at each node), within the resultant cell lineage maps, provide a unique framework for applying bioinformatics-like query algorithms such as those used for genomic databases, and the ability to locate with high temporal resolution cell cycle phase traverse and checkpoint responses. Cells responding to pharmacologically active agents in a non-invasive manner provides a means of linking causative events with later outcomes at the molecular level and the data generated creates the opportunity for pharmacokinetic (PK) and pharmacodynamic (PD) modelling and validation of intracellular dynamics in response to drug. The dynamic motility and directionality parameters would have important implications for wound healing and requires further dissection at the molecular level to determine the mechanisms which underpins the complex cellular interplay. The lineage map importantly provides a functional map upon which other information can be linked, such as single snapshot biomarker expression, proteomic and genomic expression data.

References

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